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ORIGINAL ARTICLE

Moderate to High Levels of Cardiorespiratory Fitness Attenuate the Effects of Triglyceride to High-Density Lipoprotein Cholesterol Ratio on Coronary Heart Disease Mortality in Men

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Abstract

Objective: To examine the prospective relationships among cardiorespiratory fitness (CRF), fasting blood triglyceride to high density lipoprotein cholesterol ratio (TG:HDL-C), and coronary heart disease (CHD) mortality in men.

Methods: A total of 40,269 men received a comprehensive baseline clinical examination between January 1, 1978, and December 31, 2010. Their CRF was determined from a maximal treadmill exercise test. Participants were divided into CRF categories of low, moderate, and high fit by age group and by TG:HDL-C quartiles. Hazard ratios for CHD mortality were computed using Cox regression analysis.

Results: A total of 556 deaths due to CHD occurred during a mean ± SD of 16.6±9.7 years (669,678 man-years) of follow-up. A significant positive trend in adjusted CHD mortality was shown across decreasing CRF categories (P for trend<.01). Adjusted hazard ratios were significantly higher across increasing TG:HDL-C quartiles as well (P for trend<.01). When grouped by CRF category and TG:HDL-C quartile, there was a significant positive trend (P=.04) in CHD mortality across decreasing CRF categories in each TG:HDL-C quartile.

Conclusion: Both CRF and TG:HDL-C are significantly associated with CHD mortality in men. The risk of CHD mortality in each TG:HDL-C quartile was significantly attenuated in men with moderate to high CRF compared with men with low CRF. These results suggest that assessment of CRF and TG:HDL-C should be included for routine CHD mortality risk assessment and risk management.

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Cardiovascular disease (CVD) has long been the leading cause of death for US men, accounting for approximately 403,000 deaths annually. Approximately 52% of these deaths are due to coronary heart disease (CHD).[1] Well-established major independent CHD risk factors include an elevated low-density lipoprotein cholesterol (LDL-C) level[2-4] and physical inactivity.[5-7]

Similar to elevated LDL-C level, physical inactivity is also highly prevalent in the US population.[8,9] Most studies that have examined the association between physical activity and CVD mortality have used self-reported assessment of physical activity habits.[5,10,11] Cardiorespiratory fitness (CRF) is an important variable that is related to physical activity; CRF is a physiologic characteristic that quantifies the ability of the body to transport and use oxygen at the working muscle. It is dependent primarily on maximal cardiac output, maximal arteriovenous oxygen difference, and efficient shunting of blood to working skeletal muscle.[12] Although there are data regarding the association between objective measures of CRF, CVD,[6,13-16] and CHD[17-19] mortality, the mechanisms by which higher levels of CRF independently confer decreased CHD mortality risk remain elusive.

In 2012, we reported on the individual and joint associations among CRF, LDL-C,

For editorial comment, see page 1743; for a related article, see page 1753

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and CHD mortality in men.[17] Both CRF and LDL-C were found to be significantly associated with CHD mortality. The novel finding in this study was that CHD mortality was significantly reduced across increasing levels of CRF in all LDL-C categories. We concluded that measurement of CRF should be considered for routine cardiovascular risk assessment and risk management and that men with low CRF should be encouraged to achieve at least a moderate level of CRF, regardless of LDL-C status.

Beyond high LDL-C levels, the physicochemical characteristics of LDL-C have also been implicated in risk of CHD. Low-density lipoprotein cholesterol is composed of 1 apolipoprotein B per particle, and LDL-C content varies per particle.[20] A high number of LDL-C particles or small LDL (phenotype non-A) is a characteristic of atherogenic dyslipidemia,[21] a type of dyslipidemia associated with moderate elevation of plasma triglyceride (TG) levels or low high-density lipoprotein cholesterol (HDL-C) levels.[22] Atherogenic dyslipidemia is also prevalent in patients with metabolic syndrome and those with type 2 diabetes.[23] A proxy of atherogenic dyslipidemia is the ratio of TG:HDL-C.[21]

We have shown that the TG:HDL-C is a strong and independent predictor of CHD, CVD, and all-cause mortality.[24] In a sample of 39,447 male patients from The Cooper Clinic who were followed for an average of 14.7 years, men with a high baseline TG:HDL-C ($\geq$3.5)[25] had significantly higher adjusted mortality rates than men with a normal TG:HDL-C ($<$3.5). A secondary analysis of 22,215 men in this population showed the incidence of type 2 diabetes to be significantly higher in men with a high baseline TG:HDL-C than in men with a normal ratio; this outcome was consistent across different categories of baseline fasting glucose levels. Although 55% of men with a high TG:HDL-C had metabolic syndrome, this condition was seen in only 8% of men with a normal TG:HDL-C.

We also examined the relation of TG:HDL-C and CRF in a cohort of 13,954 men from The Cooper Clinic who underwent a maximal treadmill exercise test.[26] The objective was to determine the prevalence and incidence of a high TG:HDL-C ($\geq$3.5) in men in various categories of CRF. The mean TG:HDL-C and the prevalence of a high TG:HDL-C was significantly and inversely associated with CRF in this cohort. In addition, men with low CRF and a normal TG:HDL-C ratio at baseline were 2.77 times more likely to convert to a high TG:HDL-C during mean follow-up of 5.1 years compared with men with high CRF and a normal TG:HDL-C at baseline.

We now want to examine the hypothesis that higher levels of CRF may be protective against CHD mortality in different TG:HDL-C categories. Currently, data regarding these types of associations are sparse. Thus, the purpose of the present investigation was to examine the individual and joint associations of CRF and TG:HDL-C categories with CHD mortality in a cohort of apparently healthy men.

METHODS

Study Participants and Measurements

Participants in the present study included 40,269 men aged 20 to 80 years who completed comprehensive baseline examinations at The Cooper Clinic in Dallas, Texas, between January 1, 1978, and December 31, 2010. Although The Cooper Clinic opened in 1971, measurement of HDL-C and LDL-C did not commence until 1978.

Most participants ($\sim$90%) were white and from middle to upper socioeconomic strata. The Cooper Clinic patients are either self-referred or referred by their primary care physician. The study was reviewed and approved annually by the institutional review board at The Cooper Institute. After completing written informed consent, each participant received a clinical evaluation consisting of a physician examination, fasting blood chemistry assessment, personal and family health histories, anthropometry, resting blood pressure measurement and electrocardiography, and a maximal graded treadmill exercise test.[17] Height and weight were measured using a stadiometer and a standard physician's scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference was measured at the level of the umbilicus using a cloth tape measure. The TG:HDL-C was calculated by dividing the fasting blood TG value by the fasting HDL-C value.

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